growth cone at the CNS midline will help our understanding of the mechanisms of cell motility in general.

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105

Neogenin interacts with RGMa and Netrin-1 to guide axons within the embryonic vertebrate forebrain

Nicole H. Wilson, Brian Key
University of Queensland, Brisbane, Australia

In the embryonic forebrain, pioneer axons establish a simple topography of dorsoventral and longitudinal tracts. The cues used by these axons during the initial formation of the axon scaffold remain largely unknown. We have investigated the axon guidance role of Neogenin, a member of the immunoglobulin superfamily that binds to the chemoattractive ligand Netrin-1, as well as to the chemorepulsive ligand Repulsive Guidance Molecule (RGMa). Here, we show strong mRNA expression of Neogenin and both of its putative ligands in the developing *Xenopus* forebrain. Neogenin loss-of-function mutants revealed that this receptor was essential for axon guidance in an early forming dorsoventral brain pathway. Similar mutant phenotypes were also observed following loss of either RGMa or Netrin-1. Simultaneous partial knock downs of these molecules revealed dosage-sensitive interactions and confirmed that these receptors and ligands were acting in the same pathway. The results provide the first evidence that Neogenin acts as an axon guidance molecule *in vivo*, and support a model whereby Neogenin-expressing axons respond to a combination of attractive and repulsive cues as they navigate their ventral trajectory.

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106

Neuropilin 2/semaphorin 3F signaling guides peripheral nervous system segmentation

Laura S. Gammill, Constanza Gonzalez, Marianne Bronner-Fraser
California Institute of Technology, Pasadena, CA, USA

The first indication of peripheral nervous system segmentation in vertebrates is the patterned migration of neural crest cells in streams adjacent to even-numbered rhombomeres in the head and through the anterior portion of each somite in the trunk. Later, spinal cord motor axons also extend into the anterior somite only. The cues that guide neural crest migration and projecting axons in these stereotypical, segmental patterns were not understood. We demonstrate that neural crest cells express the *receptor neuropilin 2 (Npn2)*, while its repulsive ligand *semaphorin 3F (Sema3F)* is restricted to cranial neural crest-free zones and the posterior somite. In *Npn2* and *Sema3F* mutant mice, bridges of neural crest cells cross between cranial streams, and the resulting trigeminal ganglion is loosely condensed. In the trunk, neural crest migrates uniformly through the somite and the segmental pattern of neural crest migration is abolished, although somite polarity itself remains unchanged. Furthermore, Npn2 is cell autonomously required for neural crest cells to avoid Sema3F in vitro. These data show that Npn2/Sema3F signaling guides neural crest migration in the head and trunk. Motor axons also lose their initial segmental trajectories in *Npn2* mutants, however, neural crest cells still condense into segmentally arranged dorsal root ganglia and motor axons still fasciculate into ventral roots. This indicates that the process of peripheral nervous system segmentation can be broken down into discrete steps, with Npn2/Sema3F signaling providing the initial guidance cue for both sensory and motor components.

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107

Pathological missense mutations in human L1-CAM are unable to rescue loss-of-function axonal pathfinding defects in *Drosophila*

Nagaraja Kakanahalli [1], Lars V. Kristiansen [1], Adams K. Skrzynski [1], Elisabeth Bock [2], Vladimir Berezin [2], Luis Garcia-Alonso [3], M. Hortsch [1]
[1] *Department of Cell and Developmental Biology, University of Michigan, Ann Arbor, MI, USA*
[2] *Institute of Molecular Pathology, University of Copenhagen, Denmark*
[3] *Inst. de Neuroci., Univ. Miguel Hernandez, San Juan de Alicante, Spain*

The human neural cell adhesion molecule L1-CAM has an important, evolutionarily conserved role in axonal pathfinding during nervous system development. Pathological mutations in the human L1-CAM gene cause neurodevelopmental defects. We analyzed seven human L1-CAM missense mutations for their ability to mediate cell adhesion in S2 cells and to direct axon pathfinding in the ocellar sensory system(OSS) of transgenic *Drosophila*. While, three L1-CAM mutant proteins exhibit wild type level of S2 cell aggregation, other mutations induced no or variable levels of cell aggregation. We show that enough human L1-CAM protein is expressed in transgenic *Drosophila* lines, but some mutant proteins are not efficiently transported to the cell surface. Finally, we tested six L1-CAM mutations for their ability to rescue L1 loss-of-function condition in the OSS. Whereas wild type human L1-CAM rescues these axonal pathfinding defects, three mutant proteins reverse them only partially and the other three are unable to rescue the phenotype. Thus, although several mutant L1-CAM proteins exhibit no functional defects *in vitro*, they are not able to fully rescue pathfinding defects *in vivo*. We speculate that these mutations affect downstream L1-CAM signaling processes, which are required for axonal pathfinding, such as the activation of receptor tyrosine kinase signaling.

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